> expression products, wherein said gene expression products are MN/CA9 polypeptides.
>
> Group II, claim(s) 2-7, 9-11, 14, 19-24, as specifically drawn to methods of determining prognosis comprising detecting MN/CA9 gene expression products, wherein said gene expression products are MN/CA9 polynucleotides.

[Office Action, page 2.] Applicants elect the Group I claims with traverse. Applicants reserve the right under 35 USC Section 121 to file subsequent divisional application(s) to protect the invention commensurate with the scope as originally filed.

Applicants respectfully traverse the restriction requirement, and respectfully request reconsideration and withdrawal of the restriction requirement for the reasons explained below. Applicants respectfully traverse the premise upon which the restriction requirement is based, that is, that

> [t]he inventions listed as groups I-II do not relate to a single general inventive concept . . . because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
>
> The technical feature linking groups I-II appears to be that they all relate to the special technical feature of methods of determining prognosis comprising detecting MN/CA9 gene expression products.
>
> However, Bui et al (Clinical Cancer Research, . . .) teaches methods of determining prognosis comprising detecting

> MN/CA9 gene expression products (see Table 1, in particular).
>
> Therefore, the technical feature linking the inventions of groups I-II does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.
>
> Accordingly, groups I-II are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

Applicants respectfully contest that "the special technical feature" of the instantly claimed methods "does not define a contribution over the prior art . . ." as represented by the Bui et al. article, as Applicants respectfully point out that the subject matter of Bui et al. is inapposite to that of the claimed methods.

Applicants respectfully submit that Bui et al. **is not prior art** to the instant Group I-II claimed methods, as the prognostic methods of Bui et al. 2003 are applied to one neoplastic disease, **renal clear cell carcinoma**, that is not a disease subject to the prognostic methods of the instant invention. Further, as used in Rule 13.2, "the expression 'special technical features' shall mean those technical features that define **a contribution which each of the claimed inventions, considered as a whole,** makes over the prior art." [PCT Rule 13.2; emphasis added.] Prior to the instant invention, there was no known method to determine prognosis for the genus of

diseases to which the Group I-II claims apply, comprising detecting MN/CA9 gene expression products. The pending claims 1-12, 14, 16, and 18-24 define a contribution over the prior art, and under PCT Rule 13.2 then have unity of invention.

More specifically, the instantly claimed methods are prognostic for "preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, **which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis.** . . ." [Preamble of Claim 1; emphasis added]. Exemplary preferred diseases according to the invention are preneoplastic/neoplastic diseases of the gastric mucosa [Abstract of the Invention]. In the recitation of diseases subject to methods of the instant invention, kidney diseases, including Bui et al.'s renal cell carcinoma (RCC), are absent:

> Preferably said preneoplastic/neoplastic disease afflicting the subject vertebrate is selected from the group consisting of preneoplastic/neoplastic diseases of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including ductular efferens and rete testis, ovary including surface coelomic epithelium and rete ovari, basal cells of hair follicles, and central nervous system choroid plexus.

[Instant specification, at page 7, lines 8-11.]

Further clarification of the differences between RCC and the diseases subject to the claimed methods is provided by the Introduction of the Bui et al. article:

> Previous studies using a monoclonal antibody against CAIX have shown that CAIX is induced constitutively in certain tumor types but is absent in most normal tissues with the exception of epithelial cells of the gastric mucosa. . . . Furthermore, previous immunobiochemical studies of malignant and benign renal tissues revealed that CAIX was also highly expressed in RCC, suggesting that CAIX expression may be a useful diagnostic biomarker.

[Bui et al., p. 802, col. 2, ¶2 (citations omitted); emphasis added.] In the above passage, Bui et al. are confirming that unlike RCC, "**epithelial cells of the gastric mucosa**" are an **exception to the rule of CA IX absence in normal tissues**, and therefore imply that CA IX may not be "a useful diagnostic marker" for diseases of the gastric mucosa. In that sense, Bui et al. teaches way from the instantly claimed prognostic methods.

Further, Bui et al. refer to MN/CA IX being "highly expressed in RCC" which condition is inapposite to the type of diseases which are the subject of the instant claims, that is, "a prenoplastic/neoplastic disease . . . [that] affects a tissue, which . . . **normally expresses MN/CA IX** protein, **but loses or has significantly reduced MN/CA IX expression upon carcinogenesis**. . . ." [Preamble to claim 1; emphasis added.]

For the one disease that is the subject of Bui et al., RCC, MN/CA IX is "highly expressed," whereas the diseases that are the focus of the subject invention are those in which MN/CA IX expression is lost or significantly reduced "upon carcinogenesis. . . ."

Because the prognostic methods comprising detecting MN/CA9 gene expression products in tissues that normally express MN/CA IX are fundamentally different from prognostic methods that detect MN/CA9 gene expression products in tissues that normally **do not** express MN/CA IX, Applicants respectfully point out that the Bui et al. article is not relevant to the special technical feature linking the claims of Groups I and II, when considered as a whole, according to PCT Rule 13.2, i.e., methods of determining prognosis of **diseases in tissues that normally express MN/CA IX** comprising detecting MN/CA9 gene expression products. When considered as a whole, including the distinguishing group of diseases to which the instant claims apply, the "special technical features" of the Group I-II claims defines a contribution over the prior art. Applicants respectfully submit that the inventions of Groups I and II therefore form a single general inventive concept.

Applicants respectfully request reconsideration of the subject restriction requirement in view of the above remarks, and withdrawal of the restriction requirement.

CONCLUSION

Applicants respectfully conclude that the premise upon which the subject Restriction Requirement is based, has been shown to be mistaken for the reasons explained above. Applicants respectfully request reconsideration and withdrawal of the restriction requirement.

If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,

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